

## REMARKS

### Status of the Claims

Claims 1 to 23 are pending.

In response to the Restriction Requirement dated October 3, 2001, Applicants elected Group I, claims 1 to 8, drawn to computer-implemented methods of generating a 3-D representation of a target sequence wherein the entire target sequence is listed, classified in Class 702, subclass 19.

At entry of Applicants' amendment October 22, 2002, claims 1 to 8 and 14 to 23 were pending and under consideration.

### *Claim canceled, added and amended*

Claims 1 to 8 are canceled without prejudice, claims 24 and 25 are added and claims 14 to 16 are amended in the instant response. Thus, after entry of the instant amendment, claims 14 to 25 will be pending and under consideration.

### *Outstanding Rejections*

Claims 1 to 8 and 14 to 23 are newly rejected under 35 U.S.C. 102(a) as allegedly anticipated by Kolinski et al., Proceedings of HRCL Workshop on Monte Carlo Approach to Biopolymers and Protein Folding. P. Grassberger et al., Eds., World Scientific, Singapore/London, pages 100-130 (hereinafter "Kolinski, HRCL Workshop").

Claims 1 to 8 and 14 to 23 are newly rejected under 35 U.S.C. 102(a) as allegedly anticipated by Kolinski et al., J. Phys. Chem. (1998) Vol. 102, pages 4628-4637 (hereinafter "Kolinski, J. Phys. Chem.").

Claims 1 to 8 and 14 to 23 are newly rejected under 35 U.S.C. 102(a) as allegedly anticipated by Oritz et al., Proceedings of III-rd Pacific Symposium on Biocomputing (1998), Altman et al., Eds., World Scientific Pub., Singapore/London, pages 377-388 (hereinafter "Oritz").

Claims 1 to 8 and 14 to 23 are newly rejected under 35 U.S.C. 102(b) as allegedly anticipated by Artymiuk, J. Mol. Bio. (1994) Vol. 243, pages 327-344 (hereinafter "Artymiuk").

Applicants respectfully traverse all outstanding objections to the specification and rejections of the claims.

### Support for the Claim Amendments

The specification sets forth an extensive description of the invention in the new claims. Support for claims directed to computer-assisted method for determining a three-dimensional structure of a target amino acid by producing from an alignment a three dimensional reduced protein model comprising representations of side chains of amino acid residues comprising a target protein, wherein said representations of side chains of amino acid residues are converted to interaction centers, and each interaction center comprises a pseudoatom representing a center of mass of the side chain of the represented amino acid to which the interaction center corresponds, and each interaction center is connected to an immediately proximal interaction center and an immediately distal interaction center via a virtual covalent bond to produce an interaction center chain, and then secondary constraints and/or tertiary constraints are applied to a subset of, or all of, the interaction centers of the interaction center chain so as to produce a data set representing a three-dimensional model structure of the target protein can be found, inter alia, on page 10, lines 6 to 32. Support for claims directed to computer-assisted method for determining a three-dimensional structure of a target amino acid, where the method comprises producing a data set representing a three-dimensional model structure of the target protein comprises determining side chain center of mass positions of amino acid residues of the target protein by generating a force field comprising short-range interactions that reflect secondary structure propensities and short-range packing biases, can be found, inter alia, on page 31, lines 7 to 18.

### Drawings

Corrected drawings addressing Form PTO-948 are attached. The specification has been amended to indicate that Figures 8 and 9 are now Figures 8A, 8B and Figures 9A, 9B.

### Issues under 35 U.S.C. §102

*Kolinski, HRCL Workshop*

Claims 1 to 8 and 14 to 23 are newly rejected under 35 U.S.C. 102(a) as allegedly anticipated by Kolinski, HRCL Workshop.

The legal standard for anticipation under 35 U.S.C. §102 is one of strict identity. To anticipate a claim, a single prior source must contain each and every limitation of the claimed invention.

The Patent Office alleges that Kolinski, HRCL Workshop discloses, inter alia, a model that employs a high coordination lattice representation of protein conformation space, in which side chains are treated in an explicit way, using a MONSSTER algorithm. The Patent Office further alleges that Kolinski, HRCL Workshop discloses, inter alia, a method where centers of mass of side chains of proteins serve as interaction centers, which can be represented as pseudoatoms. It is also noted that Kolinski, HRCL Workshop discloses that secondary and tertiary constraints are applied to data, and, in one aspect, identification of lowest energy structures (lowest energy conformation of a target protein).

Applicants respectfully aver that Kolinski, J. Phys. Chem. does not describe a computer-assisted method for determining a three-dimensional structure of a target amino acid sequence by aligning a target amino acid sequence with a template amino acid sequence and producing from the alignment a three dimensional reduced protein model comprising representations of side chains of amino acid residues comprising a target protein, wherein said representations of side chains of amino acid residues are converted to interaction centers and each interaction center comprises a pseudoatom representing a center of mass of the side chain of the represented amino acid to which the interaction center corresponds, and each interaction center is connected to an immediately proximal interaction center and an immediately distal interaction center via a virtual covalent bond to produce an interaction center chain, which is projected onto an underlying cubic lattice to produce a projected chain of interaction centers, and then secondary constraints and/or tertiary constraints are applied to a subset of, or all of, the interaction centers of the interaction center chain to generate a force field comprising short-range interactions, thereby producing a data set representing a three-dimensional model structure of the target protein.

Kolinski, HRCL Workshop discloses a model where tertiary restraints and loosely defined secondary structure are superimposed on top of a more general force field of the model. This force field consists of short-range interactions, generic long-range interactions and sequence specific long-range interactions. (see, e.g., the paragraph spanning pages 120 to 121 of Kolinski, HRCL Workshop).

In contrast, the methods of the instant invention use a force field designed entirely of a "knowledge-based" origin. It is noted that some terms, such as the generic short- and long-range potentials, provide a bias toward protein-like short- and long-range correlations (see page 41, lines 29 to 31 of the specification). It is noted that the force used in the methods of the invention approximately reproduce the main features of globular proteins, and does so in a different geometrical context, namely, using pseudoatoms representing side chain centers of mass. Moreover, the instant invention is based on a less complex representation and simpler definition of the force field, and is more computationally efficient than C-alpha-based models, such as MONSSTER (see page 43, lines 1 to 11, of the specification).

Kolinski, HRCL Workshop does not produce an interaction center chain and project the interaction center chain onto an underlying cubic lattice to produce a projected chain of interaction centers by using a calculated force field comprising short-range interactions as set forth in the specification, as discussed above. Accordingly, because Kolinski, HRCL Workshop is not a single prior source that contains each and every limitation of the claimed invention this rejection 35 U.S.C. 102(a) can be withdrawn.

*Kolinski, J. Phys. Chem.*

Claims 1 to 8 and 14 to 23 are newly rejected under 35 U.S.C. 102(a) as allegedly anticipated by Kolinski, J. Phys. Chem.

The legal standard for anticipation under 35 U.S.C. §102 is one of strict identity. To anticipate a claim, a single prior source must contain each and every limitation of the claimed invention.

The Patent Office alleges that Kolinski, J. Phys. Chem. has incorporated the idea of side chain representation into computer modeling techniques for protein structure, and that the lattice chains of centers of mass of side chains is employed which utilizes Monte Carlo simulation to represent the three-dimensional structure of a target polypeptide.

Applicants respectfully aver that Kolinski, J. Phys. Chem. does not describe a computer-assisted method for determining a three-dimensional structure of a target amino acid sequence by aligning a target amino acid sequence with a template amino acid sequence and producing from the alignment a three dimensional reduced protein model comprising representations of side chains of amino acid residues comprising a target protein, wherein said representations of side chains of amino acid residues are converted to interaction centers and each interaction center comprises a pseudoatom representing a center of mass of the side chain of the represented amino acid to which the interaction center corresponds, and each interaction center is connected to an immediately proximal interaction center and an immediately distal interaction center via a virtual covalent bond to produce an interaction center chain, which is projected onto an underlying cubic lattice to produce a projected chain of interaction centers, and then secondary constraints and/or tertiary constraints are applied to a subset of, or all of, the interaction centers of the interaction center chain to generate a force field comprising short-range interactions, thereby producing a data set representing a three-dimensional model structure of the target protein.

In contrast, the Kolinski, J. Phys. Chem. model “employs a single united atom representation of amino acid residues. These atoms are centered on protein side groups. Characteristic short-range distance correlations have been built into the model, thereby providing a rather accurate description of protein-like conformational stiffness. Sequence-specific interaction schemes have been derived from sequence similarity and sequence-structure compatibility studies” [emphasis added] (see abstract). The Kolinski, J. Phys. Chem. model “employ[s] only the homology ... of small fragments of protein sequences, thereby allowing for the construction of a potential for sequences having no globally homologous counterparts in the structural database.” [emphasis added] (see page 4628, right-hand column, last sentence first full paragraph); and, “[t]he purpose of this work is to analyze the role of the generic protein-like regularities seen in protein chains, the role of sequence-specific short-range correlations of the

side chain positions, and this interplay.” [emphasis added] (see the sentence spanning pages 4628 and 4629)

Kolinski, J. Phys. Chem. does not produce an interaction center chain and project the interaction center chain onto an underlying cubic lattice to produce a projected chain of interaction centers by using a calculated force field comprising short-range interactions. Accordingly, because Kolinski, J. Phys. Chem. is not a single prior source that contains each and every limitation of the claimed invention this rejection 35 U.S.C. 102(a) can be withdrawn.

*Oritz*

Claims 1 to 8 and 14 to 23 are newly rejected under 35 U.S.C. 102(a) as allegedly anticipated by Ortiz.

The legal standard for anticipation under 35 U.S.C. §102 is one of strict identity. To anticipate a claim, a single prior source must contain each and every limitation of the claimed invention.

The Patent Office alleges that Ortiz discloses a method that uses restraints derived from multiple sequence alignments combined with fold assembly algorithm to predict protein structure and that Figure 1 (of Ortiz) outlines the basis of the method and is virtually identical to Figure 15 in the instant application. The Patent Office also alleges that Ortiz describes the MONSSTER algorithm disclosed in the instant application and describes the methods as listed above that encompass embodiments of the instant invention.

Applicants respectfully aver that Ortiz does not describe a computer-assisted method for determining a three-dimensional structure of a target amino acid sequence by aligning a target amino acid sequence with a template amino acid sequence and producing from the alignment a three dimensional reduced protein model comprising representations of side chains of amino acid residues comprising a target protein, wherein said representations of side chains of amino acid residues are converted to interaction centers and each interaction center comprises a pseudoatom representing a center of mass of the side chain of the represented amino acid to which the interaction center corresponds, and each interaction center is connected to an immediately proximal interaction center and an immediately distal interaction center via a virtual covalent bond to produce an interaction center chain, which is projected onto an underlying

cubic lattice to produce a projected chain of interaction centers, and then secondary constraints and/or tertiary constraints are applied to a subset of, or all of, the interaction centers of the interaction center chain to generate a force field comprising short-range interactions, thereby producing a data set representing a three-dimensional model structure of the target protein.

In contrast, Ortiz's method incorporates "predicted secondary and tertiary restraints into *ab initio* folding simulations" to generate "low resolution tertiary structures" of nonhomologous proteins. Ortiz states "[s]econdary structural restraints are provided by the PHD secondary structure prediction algorithm that incorporates multiple sequence information. Predicted tertiary restraints are obtained from multiple sequence alignments via a two-step process: First, "seed" side chain contacts are identified from a correlated mutation analysis, and then, the seed contacts are "expanded" by an inverse folding algorithm. These predicted restraints are then incorporated into a lattice based, reduced protein model. Depending upon fold complexity, the resulting native-like topologies exhibit a coordinate root-mean-square deviation, cRMSD, from native between 3.1 and 6.7 Å. Overall, this study suggests that the use of restraints derived from multiple sequence alignments combined with a fold assembly algorithm is a promising approach to the prediction of the global topology of small proteins. [emphasis added] (see abstract of Ortiz). Ortiz explores whether use of predicted secondary structure and tertiary restraints are adequate to predict tertiary structure from sequence alone [emphasis added] (see left-hand column, page 378, of Ortiz).

Ortiz does not produce an interaction center chain and project the interaction center chain onto an underlying cubic lattice to produce a projected chain of interaction centers by using a calculated force field comprising short-range interactions. Accordingly, because Ortiz is not a single prior source that contains each and every limitation of the claimed invention this rejection 35 U.S.C. 102(a) can be withdrawn.

*Artymiuk*

Claims 1 to 8 and 14 to 23 are newly rejected under 35 U.S.C. 102(b) as allegedly anticipated by Artymiuk.

The legal standard for anticipation under 35 U.S.C. §102 is one of strict identity. To anticipate a claim, a single prior source must contain each and every limitation of the claimed

invention.

The Patent Office alleges, inter alia, that Artymiuk discloses a computer program called ASSAM that is designed to allow location of all occurrences of user-defined pattern of residues in all of the structures in the Protein Databank. The Patent Office also alleges that in Artymiuk the residues of interest in the target protein are defined in geometric terms using a simplified representation of the side-chain, meeting the limitations of claim 1 and 14.

Applicants respectfully aver that Artymiuk does not describe a computer-assisted method for determining a three-dimensional structure of a target amino acid sequence by aligning a target amino acid sequence with a template amino acid sequence and producing from the alignment a three dimensional reduced protein model comprising representations of side chains of amino acid residues comprising a target protein, wherein said representations of side chains of amino acid residues are converted to interaction centers and each interaction center comprises a pseudoatom representing a center of mass of the side chain of the represented amino acid to which the interaction center corresponds, and each interaction center is connected to an immediately proximal interaction center and an immediately distal interaction center via a virtual covalent bond to produce an interaction center chain, which is projected onto an underlying cubic lattice to produce a projected chain of interaction centers, and then secondary constraints and/or tertiary constraints are applied to a subset of, or all of, the interaction centers of the interaction center chain to generate a force field comprising short-range interactions, thereby producing a data set representing a three-dimensional model structure of the target protein.

In contrast, Artymiuk "searches for patterns of side-chains" (see abstract) by defining "the relative orientations of side-chains in space by means of distances ... between pseudo-atoms represented the side-chain." [emphasis added] (see page 329, right-hand column, beginning 17 lines down from the top of the column). In Artymiuk's method the "pseudoatom representation of a protein is a graph in which the nodes are the vectors joining the pseudo-atoms and the edges are the set of distances." [emphasis added] (see page 329, right-hand column, beginning 28 lines down from the top of the column). Artymiuk concludes "The residues in a protein or a query pattern are represented in a highly simplified form that consists of two pseudo-atoms, and the relative orientations of pairs of side-chains are defined by the distances between pairs of these pseudo-atoms." [emphasis added] (see page 339, conclusion section, first



paragraph).

Artymiuk does not produce an interaction center chain and project the interaction center chain onto an underlying cubic lattice to produce a projected chain of interaction centers by using a calculated force field comprising short-range interactions. Accordingly, because Artymiuk is not a single prior source that contains each and every limitation of the claimed invention this rejection 35 U.S.C. 102(a) can be withdrawn.

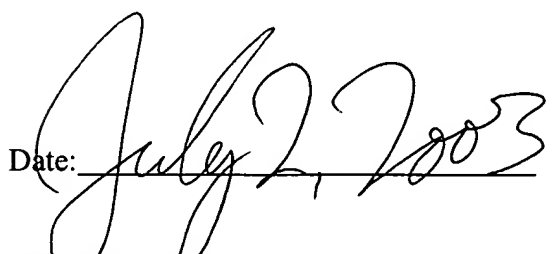
### CONCLUSION

In view of the foregoing amendment and remarks, it is believed that the Examiner can properly withdraw the rejection of the pending claims under 35 U.S.C. §102(a) and (b). Applicants believe after entry of the instant amendment all claims pending in this application will be in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

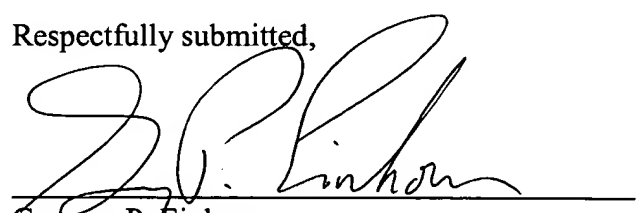
If necessary, please apply additional and necessary charges, and apply all credits, to Deposit Account No. 06-1050.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (858) 678-5070.

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